



# Drug and Alcohol Dependence

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Full length article

## Sustained reduction of diversion and abuse after introduction of an abuse deterrent formulation of extended release oxycodone



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### ABSTRACT

**Background:** The development of abuse deterrent formulations is one strategy for reducing prescription opioid misuse and abuse. A putative abuse deterrent formulation of oxycodone extended release (OxyContin<sup>®</sup>) was introduced in 2010. Early reports demonstrated reduced abuse and diversion, however, an analysis of social media found 32 feasible methods to circumvent the abuse deterrent mechanism. We measured trends of diversion, abuse and street price of OxyContin to assess the durability of the initial reduction in abuse.

**Methods:** Data from the Poison Center Program, Drug Diversion Program, Opioid Treatment Program, Survey of Key Informant Patients Program and StreetRx program of the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS<sup>®</sup>) System were used. The average quarterly rates of abuse and diversion for OxyContin were compared from before reformulation to the rate in second quarter 2015. Rates were adjusted for population using US Census data and drug availability.

**Results:** OxyContin abuse and diversion declined significantly each quarter after reformulation and persisted for 5 years. The rate of abuse of other opioid analgesics increased initially and then decreased, but to lesser extent than OxyContin. Abuse through both oral and non-oral routes of self-administration declined following the reformulation. The geometric mean difference in the street price of reformulated OxyContin was 36% lower than the reformulated product in the year after reformulation.

**Discussion:** Despite methods to circumvent the abuse deterrent mechanism, abuse and diversion of OxyContin decreased promptly following the introduction of a crush- and solubility- resistant formulation and continued to decrease over the subsequent 5 years.

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### 1. Introduction

Misuse and abuse of prescription analgesics is a major health problem. In 2014, there were 2.2 million current nonmedical

users of prescription pain relievers in the United States (Center for Behavioral Health Statistics and Quality, 2015). More than 16,000 deaths were attributed to prescription pain relievers in 2013 (Hedegaard et al., 2015). In 2011, the Office of National Drug Control Policy issued a national strategy to combat prescription drug abuse (United States Office of National Drug Control Policy, 2011). The strategy included several components, including research into formulations with abuse deterrent properties. In 2015, the FDA released guidance regarding the development of abuse deterrent formulations (United States Food and Drug Administration, 2015). One specified property was physical-chemical barriers, which involves making a tablet difficult to crush; thereby inhibiting use through chewing, nasal insufflation, injection, or smoking.

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OxyContin® is an extended release (ER) formulation of oxycodone that became a popular drug of abuse (United States Food and Drug Administration, 2001). In 2010, the manufacturer introduced a reformulated tablet that was difficult to crush and formed a viscous hydrogel to make snorting and injection difficult (Alexander et al., 2014). The FDA approved new labeling describing the abuse deterrent features and subsequently denied applications from other oxycodone ER formulations without abuse deterrent features (United States Food and Drug Administration, 2013). Reformulated OxyContin and its authorized generic products remain the only form of oxycodone ER marketed in the United States.

Initial reports suggested that reformulation reduced the abuse and diversion of OxyContin (Severtson et al., 2013; Butler et al., 2013). However, a review of internet forums found 32 feasible recipes to overcome the tamper resistant properties (McNaughton et al., 2014). Previous research suggests that many abusers switch to other products, particularly immediate release oxycodone and hydromorphone (Cicero et al., 2012; Havens et al., 2014). If methods to circumvent abuse deterrent methods became widespread, abuse and diversion could return to high rates. OxyContin represents a sentinel opportunity to assess the durability of the strategy of physical-chemical abuse deterrent properties.

We analyzed rates of opioid analgesic abuse and diversion for the 5 years following reformulation to determine whether initial reductions in OxyContin abuse persisted despite the availability of methods to circumvent the abuse deterrent properties.

## 2. Methods

### 2.1. Data sources

The Researched, Abuse, Diversion, and Addiction Related Surveillance (RADARS®) System provides post-marketing surveillance of prescription medication abuse and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. The System is comprised of multiple surveillance programs that independently gather data on prescription drug abuse from different perspectives. The RADARS System is owned and operated by the Denver Health and Hospital Authority, which operates the public hospital for the city and county of Denver. The system is supported by subscriptions from pharmaceutical companies that produce prescription opioids or stimulants, which use the data for risk management and postmarketing surveillance reporting to the Food and Drug Administration.

The Poison Center Program studies acute health events by recording the substances involved in poison center cases classified as intentional abuse. The Drug Diversion Program measures drug diversion by recording the drugs involved in cases opened by law enforcement drug diversion investigators. The Opioid Treatment Program and the Survey of Key Informants' Patients Program both query new patients entering substance-abuse treatment about medications that they have abused. The StreetRx Program utilizes a crowdsourcing website that gathers street price data for drugs using a publically-accessible website. Further information on each surveillance program has been published (Dart et al., 2015).

### 2.2. Definitions

In the Poison Center Program, a *case* involves an individual exposure contact in which the case was coded to the category of Intentional Abuse, which is defined as an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a euphoric or other psychotropic effect (American Association of Poison Control Centers,

2014). Poison Center Program *mentions* are the total number of active pharmaceutical ingredient (API) reports involved for all cases within a defined group. Mentions differ from cases in that an individual (case) may be exposed to more than one product (mention). There is an average of 1.04 opioid mentions per case.

In the Opioid Treatment and Survey of Key Informants' Patients programs, a case is defined as a survey respondent endorsing the abuse of a prescription opioid in the preceding 30 days. In these programs, *mentions* are the total number of endorsements. The average number of mentions per case is 1.68 for the Opioid Treatment Program and 1.83 for the Survey of Key Informant Patients Program.

In the Drug Diversion Program, a case is defined as an investigation, which can have one or more mentions (drugs involved in the case). Drug diversion officers submit data quarterly on the number of new cases involving prescription products within their jurisdiction. These cases arise from arrests, street buys and sales by law enforcement agents, and investigation of prescribers, among other reasons.

In StreetRx, users enter the price of drugs they paid or heard was paid from an extensive list of drugs provided on the website (<http://streetrx.com>). StreetRx submissions from the United States for OxyContin that included a price paid, dosage strength, and date were included.

Quarterly population rates were calculated by dividing the total number of cases by the sum of the population in the 3-digit ZIP codes covered by each program using 2010 US census results, thus allowing for each individual to contribute once to the numerator and once to the denominator within each drug group. In contrast, rates adjusted for prescriptions dispensed are calculated by dividing the sum of the mentions by the sum of the projected prescription volume in the 3-digit ZIP codes covered by each program. For mention based rates, such as prescription rates, a single individual may be counted multiple times in both the numerator and denominator. Quarterly prescription rates were calculated using the projected number of prescriptions dispensed as provided using a proprietary method by IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc. (Danbury, CT) for each drug. Due to preferences indicated by US FDA, we also calculated rates using the concept of "extended dosage units," which is defined as individual tablets or capsules dispensed at retail pharmacies (IMS Government Solutions, Danbury CT; Secora et al., 2014).

### 2.3. Analysis procedures

Generalized linear modeling was used to compare the difference in mean population intentional abuse and diversion rates in the year prior to the reformulation (Baseline period: July 2009 through June 2010) to the estimated rate for 2015 quarter (2Q, April 2015 through June 2015) based upon the trend (slope) of the post-reformulation rates. Changes in the OxyContin rate were compared to changes for the Other Opioid group (oral dosage forms of opioid analgesics: hydrocodone, hydromorphone, morphine, oxymorphone, tramadol, tapentadol, and immediate release oxycodone). The group was chosen because published evidence indicates that abusers switch to a variety of other prescription opioid analgesics, therefore, we combined the oral dosage unit formulation of those products into a single comparison group (Cicero et al., 2012; Havens et al., 2014). Oxymorphone data were only available from 2011 in the Drug Diversion program and from 2011 Q3 in the Opioid Treatment and Survey of Key Informants' Patients Programs. A Poisson regression analysis was used to calculate the expected rates and 95% confidence bands for each time period and drug group. A drug group specific dispersion parameter was included in the model to allow for unequal variances and overdispersion. The six month period encompassing the introduction of

**Table 1**  
Change in rate of abuse and diversion for prescription opioids after reformulation of OxyContin.

	Population Adjusted			Prescription Adjusted		
	Baseline rate per 100,000 population	Projected rate in 2015–Q2 per 100,000 population	Total change 2015–Q2 (%) 95% CI	Quarterly Rate change (%)	Baseline rate per 1000 prescription dispensed	Projected rate in 2015–Q2 per 1000 prescriptions dispensed
Poison Center Program						
OxyContin	0.056	0.014	–75.0 <sup>a</sup> –78.4, –71.1	–6.1 <sup>a</sup> –7.1, –5.1	0.100	0.038
Other Opioid Group	0.387	0.260	–32.8 –37.4, –27.9	–3.1 –3.5, –2.6	0.023	0.015
Drug Diversion Program						
OxyContin	0.195	0.021	–89.4 <sup>b</sup> –92.6, –85.2	–8.9 <sup>a</sup> –11.2, –6.5	0.386	0.055
Other Opioids	1.344	0.983	–26.8 –36.0, –16.3	–2.8 –3.7 to –1.9	0.085	0.058
Opioid Treatment Program						
OxyContin	0.574	0.100	–82.6 <sup>b</sup> –86.7, –77.1	–9.4 <sup>a</sup> –11.1, –7.6	0.962	0.261
Other Opioid Group	0.986	0.670	–32.0 –40.1, –22.9	–3.5 –4.3, –2.7	0.116	0.080
Survey of Key Informants' Patients						
OxyContin	0.265	0.122	–53.9 <sup>a</sup> –64.1, –40.7	–4.0 <sup>c</sup> –5.5, –2.4	0.495	0.323
Other Opioid Group	0.475	0.441	–7.2 –19.4, 6.9	–1.5 –2.3, –0.7	0.058	0.065
CI – confidence intervals.						
IR – immediate release formulation.						
ER – extended release formulation.						
Other Opioid Group = (IR oxycodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxycodone, and IR and ER tapentadol).						

CI – confidence intervals.

IR – immediate release formulation.

ER – extended release formulation.

Other Opioid Group = (IR oxycodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxycodone, and IR and ER tapentadol).

<sup>a</sup> Significantly different from other opioids,  $p < 0.0001$ .<sup>b</sup> Significantly different from other opioids,  $p < 0.001$ .<sup>c</sup> Significantly different from other opioids,  $p < 0.01$ .

reformulated OxyContin was considered a transition period and excluded from the analysis. Therefore, quarterly rates from July, 2009 to June, 2010 (before reformulation) and rates from January, 2011 to June, 2015 (after reformulation) were used in all analyses.

The route of administration for poison center cases was compared before and after introduction of reformulated OxyContin using generalized linear modeling. Comparisons were conducted by route of administration and by time period. Oral routes (swallowing tablet whole, dissolving in mouth, and chewing then swallowing) were compared to non-oral routes (injection or inhalation, which is primarily insufflation). A specific dispersion parameter for route of OxyContin administration was included in the model. Product specific route information was collected beginning in January, 2010; therefore the analysis period includes quarterly rates from January, 2010 to June, 2010 (before reformulation) and January, 2011 to June, 2015 (after reformulation).

Street price data were normalized by the milligram strength of the unit purchased, providing price per milligram as the analysis metric. The price data from the StreetRx Program were positively skewed, therefore, in multivariate models the price data were log-transformed and regressed on a covariate for year and formulation. This calculation provides a difference in the geometric mean price adjusted for time. Geometric means were used because they approximate the median and are considered more representative than arithmetic means in economic research.

### 3. Results

#### 3.1. Number of prescriptions dispensed

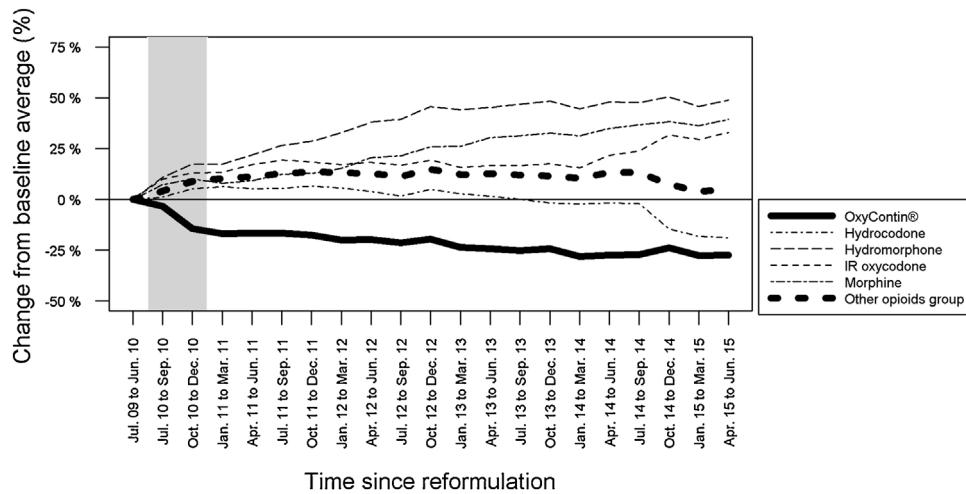
Prescriptions dispensed for OxyContin decreased from 1,608,747 in second quarter 2010 (2010–Q2) to 1,211,593 in 2015–Q2, a 25% reduction (Fig. 1). In contrast, the Other Opioid group increased 7% from 50,814,374 to 54,567,288 during the same period. Except for hydrocodone combination formulations and OxyContin, prescriptions dispensed increased for each opioid analgesic.

The decrease in prescriptions was biphasic. In the 6 month period of 2010–Q3 through 201–Q1, OxyContin prescriptions dispensed declined 13.9%, while prescriptions for Other Opioids increased 5.9%. Subsequently, for the period from 2011–Q2 through 2015–Q2, OxyContin declined 12.9% and Other Opioids declined 5.9%.

#### 3.2. Poison center program intentional abuse

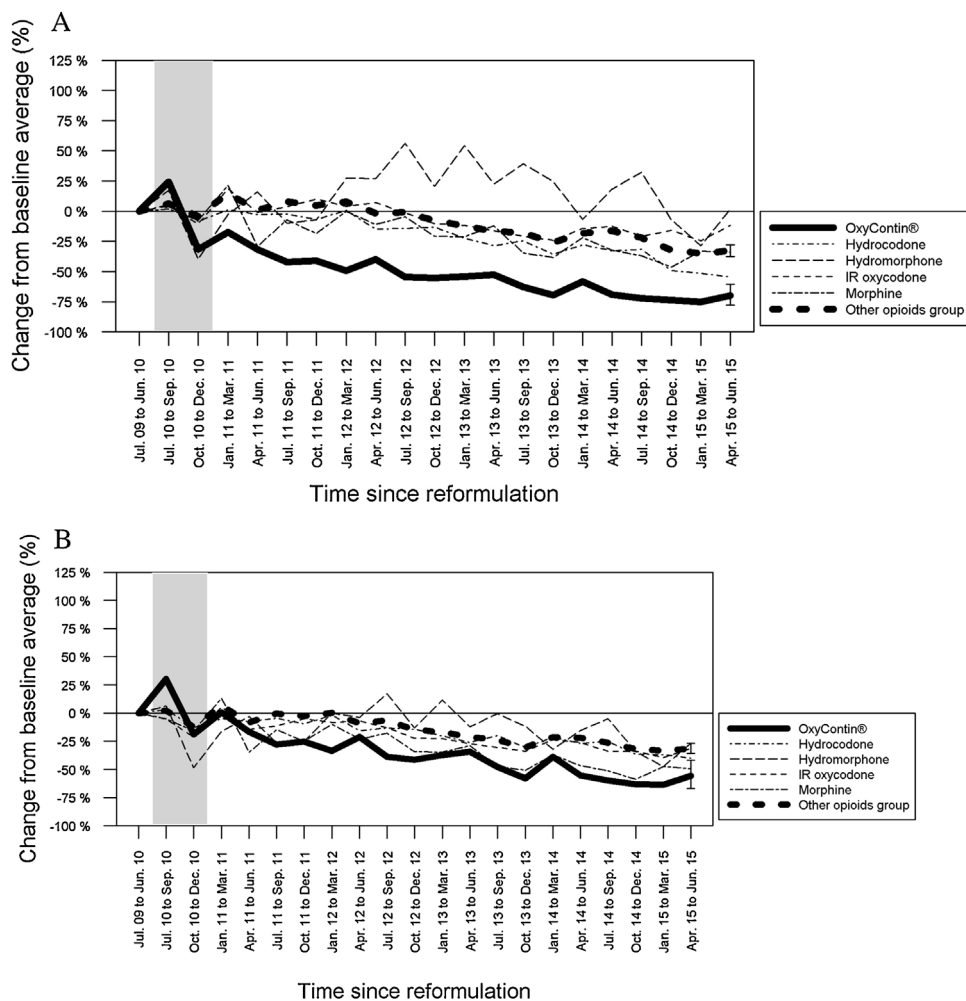
A total of 2159 OxyContin cases and 19,815 Other Opioid cases were received during the study period. The population adjusted rate for OxyContin decreased –75.0% (95% CI: –78.4, –71.1) after reformulation (Table 1, Fig. 2A), from baseline to 2015–Q2. This was the greatest decrease among the opioids and significantly larger than the Other Opioid group (–32.8%, 95% CI: –37.4, –27.9). The rate for OxyContin declined –6.1% (95% CI: –7.1% to –5.1%) each quarter on average following reformulation, which was greater than the Other Opioid group) (–3.1%, 95% CI: –3.5, –2.6).

The prescription adjusted OxyContin rate decreased –62.3% (95% CI: –67.9, –55.6) following reformulation (Table 1, Fig. 2B) from baseline to 2015–Q2, which was the greatest among the opioid categories and significantly greater than the Other Opioid group (–33.7%, 95% CI: –38.1, –29.0). OxyContin rates declined –5.0% (95% CI: –6.1%, –3.8) per quarter on average following reformulation, which was significantly greater than the Other Opioid group (–2.6%, 95% CI: –3.0, –2.2).



**Fig. 1.** Number of opioid analgesic prescriptions dispensed in the United States, April 1, 2009 to June 30, 2015. The Other Opioid Group is comprised of immediate release (IR) oxycodone, IR and extended release (ER) hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxymorphone, and IR and ER tapentadol. The period of time indicated by shading was excluded from statistical analysis.

Source: IMS Government Solutions, Inc., a subsidiary of IMS Health, Inc., Danbury, CT.



**Fig. 2.** Relative change in rate of Intentional Abuse cases, Poison Center Program, 2009–2015. The Other Opioid Group is comprised of immediate release (IR) oxycodone, IR and extended release (ER) hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxymorphone, and IR and ER tapentadol. The period of time indicated by shading was excluded from statistical analysis. CI – 95% Confidence intervals. (A) Rate adjusted for population. (B) Rate adjusted for prescription volume.



The units-dispensed OxyContin rate decreased  $-56.1\%$  (95% CI:  $-62.7, -48.3$ ) following reformulation, which was significantly greater than the Other Opioid group ( $-34.4\%$ , 95% CI  $-39.6, -28.8$ ).

### 3.3. Drug diversion program

A total of 4142 OxyContin cases and 57,135 Other Opioid cases were received during the study period. The population adjusted rate for OxyContin decreased  $-89.4\%$  (95% CI:  $-92.4, -85.2$ ) after reformulation (Table 1, Fig. 3A). The decrease was greatest of the opioid categories and statistically different than the Other Opioid group ( $-26.8\%$ , 95% CI:  $-36.0, -16.3$ ). OxyContin rates declined  $-8.9\%$  (95% CI:  $-11.2, -6.5$ ) each quarter following reformulation, which was greater than the Other Opioid group ( $-2.8\%$ , 95% CI:  $-3.7, -1.9$ ).

The prescription adjusted OxyContin rate decreased  $-85.8\%$  (95% CI:  $-89.7, -80.5$ ) after reformulation (Table 1, Fig. 3B). The decrease was greatest of the opioid categories and statistically greater than the Other Opioid group ( $-31.7\%$ , 95% CI:  $-40.3, -21.8$ ). OxyContin rates declined  $-8.3\%$  (95% CI:  $-10.6, -6.1$ ) per quarter after reformulation, which was significantly greater than the Other Opioid group ( $-3.6\%$ , 95% CI:  $-3.6, -1.8$ ).

The dosage unit adjusted rate for OxyContin decreased  $-83.4\%$  (95% CI:  $-88.0\%, -76.0\%$ ) following reformulation, which was statistically greater than the Other Opioid group ( $-33.2\%$ , 95% CI  $-42.1, -23.0$ ).

### 3.4. Opioid treatment program

A total of 8176 OxyContin cases and 15,873 Other Opioid cases were received. The population adjusted rate for OxyContin decreased  $-82.6\%$  (95% CI:  $-86.7, -77.1$ ) after reformulation from baseline to 2015-Q2 (Table 1, Fig. 4A). The decrease was greatest of the opioid categories and statistically greater than the Other Opioid group ( $-32.0\%$ , 95% CI:  $-40.1, -22.9$ ). The OxyContin rate declined  $-9.4\%$  (95% CI:  $-11.1, -7.6$ ) each quarter on average following reformulation, which was greater than the Other Opioid group ( $-3.5\%$ , 95% CI:  $-4.3, -2.7$ ).

The prescription adjusted OxyContin rate decreased  $-72.8\%$  (95% CI:  $-80.6, -62.0$ ) after reformulation from baseline to 2015-Q2 (Table 1, Fig. 4B). The decrease was greatest of the opioid categories and statistically greater than the Other Opioid group ( $-30.9\%$ , 95% CI:  $-40.4, -19.8$ ). OxyContin declined  $-8.2\%$  (95% CI:  $-10.4, -6.0$ ) per quarter on average, which was greater than the Other Opioid group ( $-3.2\%$ , 95% CI:  $-4.2, -2.3$ ).

The units dispensed OxyContin rate decreased  $-68.4\%$  (95% CI:  $-77.5\%, -55.7$ ) following reformulation, which was significantly different than the Other Opioid group ( $-31.2\%$ , 95% CI  $-41.4, -19.3$ ) lower than before the reformulation.

### 3.5. Survey of key informants' patients program

A total of 3987 OxyContin cases and 8451 Other Opioid cases were received. The population adjusted rate for OxyContin decreased  $-53.9\%$  (95% CI:  $-64.1, -40.7$ ) after reformulation from baseline to 2015-Q2 (Table 1, Fig. 5A). The decrease was greatest of the opioid categories and statistically greater than the Other Opioid group ( $-7.2\%$  (95% CI:  $-19.4, 6.9$ )). OxyContin declined  $-4.0\%$  ( $-5.5, -2.4$ ) each quarter on average following reformulation, which was significantly greater than the Other Opioid group ( $-1.5\%$ , 95% CI:  $-2.3, -0.7$ ).

The prescription adjusted OxyContin rate decreased  $-34.8\%$  (95% CI:  $-48.4, -17.7$ ) after reformulation from baseline to 2015-Q2 (Table 1, Fig. 5B). The decrease was statistically greater than the Other Opioid group (10.8% 95% CI:  $-5.1, 29.5$ ) as well as the other individual opioids, except morphine. OxyContin declined  $-2.6\%$

(95% CI:  $-4.0, -1.1$ ) per quarter, which was significantly greater than the Other Opioid group ( $-0.3\%$ , 95% CI:  $-1.1, 0.5$ ).

The units dispensed adjusted OxyContin rate decreased  $-23.8\%$  (95% CI:  $-39.8, -3.6$ ) following reformulation, which was statistically different than the Other Opioid group 9.0%, 95%CI (7.3, 28.3).

### 3.6. Route of administration

Of the 1863 OxyContin cases received from poison centers from January, 2010 to June, 2015, 1511 reported the route of use: 1057 oral and 454 non-oral. Route was not reported for the remainder. The rate of OxyContin abuse using for the oral route decreased from 0.0285 per 100,000 population before reformulation to 0.0082 in 2015-Q2, a 71.0% (95% CI:  $-76.9, -63.7$ ) reduction (Fig. 6). The non-oral route decreased from 0.0184 per 100,000 population before reformulation to 0.0025 in 2015-Q2, an 86.7% (95% CI:  $-91.9, -78.0$ ) reduction, which was significantly greater than the oral route ( $p=0.006$ ).

### 3.7. Street price

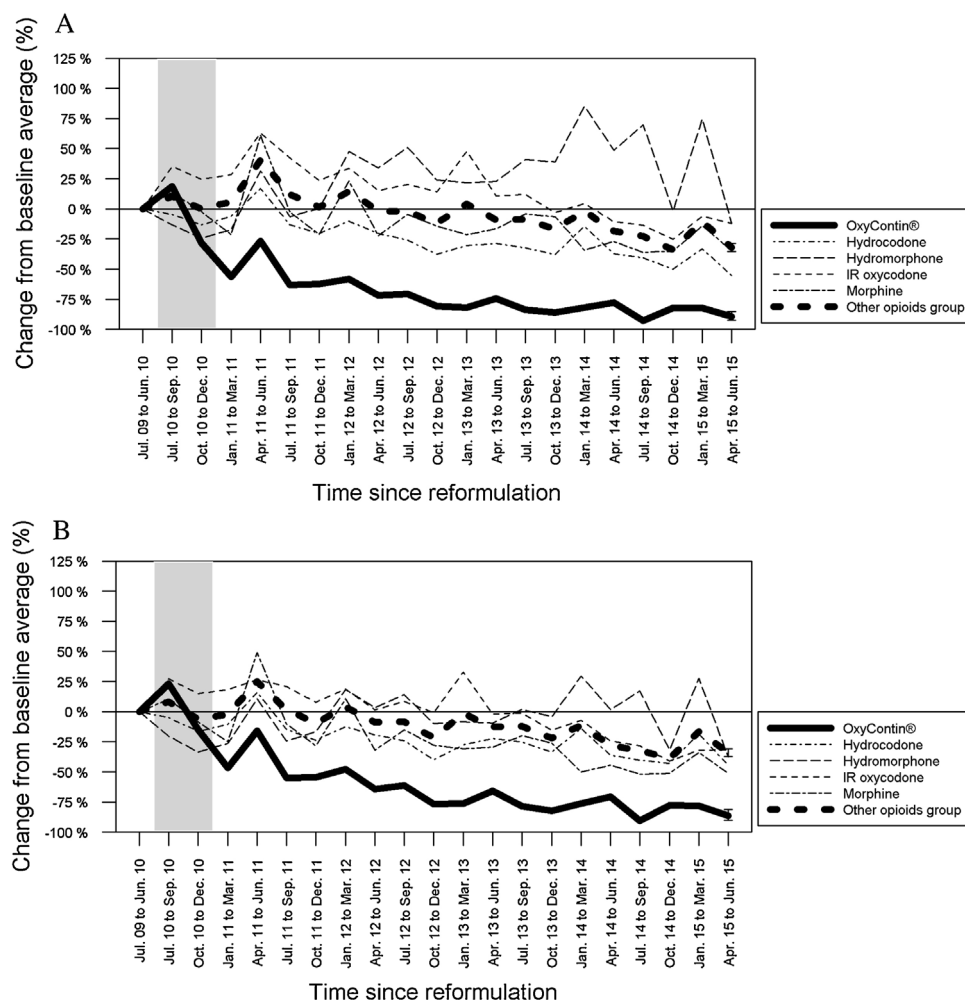
A total of 3537 street price reports for OxyContin were submitted. The price of single-entity oxycodone, original formulation OxyContin and reformulated OxyContin all decreased from 2011 through 2015. The geometric mean price of OxyContin original formulation decreased from \$1.40 to \$0.61 from 2011 to 2015, a 57% (95% CI: 37% to 70%,  $p<0.001$ ) reduction. The geometric mean price of reformulated OxyContin decreased from \$0.89 to \$0.53 from 2011 to 2015, a 41% (95% CI: 19%, 57%,  $p=0.001$ ) reduction. The difference in price for original and reformulated OxyContin was 36% in 2011 and 13% in 2015 (Fig. 7).

## 4. Discussion

The introduction of abuse deterrent formulations has created controversy regarding their value in reducing abuse of opioid analgesics. Concerns regarding abuse deterrent formulations involve 1) the potential for overprescribing because prescribers may underestimate the abuse risk of an analgesic with abuse deterrent properties, 2) dissemination of techniques to subvert an abuse deterrent mechanism and thereby allow abuse to rebound or increase, and 3) switching of abuse to other opioids or relying more heavily on oral abuse.

Concerns about escalating prescribing of OxyContin are not supported by our results. After reformulation, the number of OxyContin prescriptions dispensed decreased progressively over 5 years. This change is notable because the prescription volume for OxyContin had increased greatly since its introduction in 1996. Other investigators have documented a substantial decrease in OxyContin prescriptions following reformulation (Hwang et al., 2015; Larochelle et al., 2015).

The sudden decrease in OxyContin prescriptions dispensed suggests that there was a sudden decrease in demand. While there were likely other factors involved, a substantial decrease in a short period limits the potential influence of other factors and suggests that abusers reduced their attempts to obtain OxyContin. For most pharmaceuticals, the prescriber controls the supply of a drug, but prescription opioids are unusual because abusers can stimulate prescription writing. A decrease in the number of attempts to secure a prescription by feigning a painful condition ("doctor shoppers") could decrease the number of prescriptions dispensed, particularly in the period immediately after reformulation. The subsequent long gradual decrease in prescribing seems more likely to be influenced by factors in addition to doctor shopping, like restrictions implemented by insurers and perceptions by prescribers. Each



**Fig. 3.** Relative change in rate of Diversion Cases, Drug Diversion Program, 2009–2015. The Other Opioid Group is comprised of immediate release (IR) oxycodone, IR and extended release (ER) hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxymorphone, and IR and ER tapentadol. The period of time indicated by shading was excluded from statistical analysis. CI – 95% Confidence intervals. (A) Rate adjusted for population. (B) Rate adjusted for prescription volume.

of these reasons could potentially drive prescribers away from OxyContin and towards prescribing of other opioid analgesics.

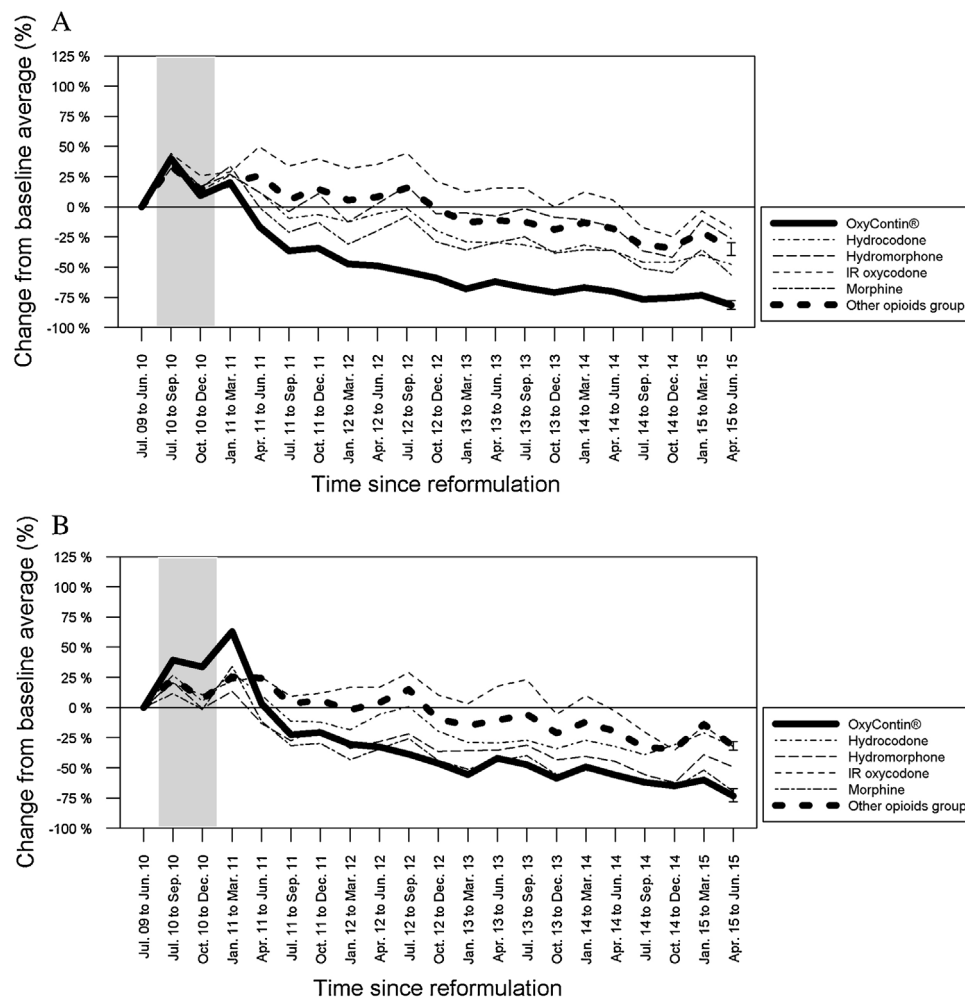
In contrast to OxyContin, the number of prescriptions dispensed for the Other Opioid Group increased from 2010 to 2012, then plateaued from 2012 to 2014, and finally decreased when hydrocodone was reclassified as a Schedule 2 controlled substance. Increased prescribing of prescription opioid analgesics is a legitimate concern, but prescription data do not indicate that OxyContin has been affected.

We found that abuse and diversion of OxyContin as measured by 4 programs decreased promptly and progressively over 5 years. In addition, the street price for the reformulated product was much lower than the original formulation. Other investigators have reported substantial reductions in OxyContin abuse after reformulation. (Buer et al., 2014; Butler et al., 2013; Coplan et al., 2013; Havens et al., 2014; Larochelle et al., 2015; Severtson et al., 2013; Sessler et al., 2014), but included much shorter periods of evaluation after reformulation. Similarly, introduction of reformulated OxyContin in Australia was followed by decreased prescribing, abuse, injection and snorting (Degenhardt et al., 2015). A dissenting view submitted to the FDA found that the endorsement of non-medical use of OxyContin in the National Survey of Drug Use and Health (NSDUH) did not differ between periods (one year before and after its reformulation; Novak, 2013). However, this analysis occurred soon after reformulation. Given the time needed for a

reformulated product to permeate the market, it is likely that the original formulation was readily accessible for much of the analysis period. Analysis of current data from NSDUH indicates trends similar to our results. After increasing from 2004 to 2010, endorsement of past year nonmedical use of OxyContin decreased 23.7% from 2011 to 2014 (Fig. 8).

Our analytic models assumed a constant effect for other interventions that were enacted during the study period, such as expansion of prescription drug monitoring plans (PDMPs), Risk Evaluation and Mitigation Strategies (REMS), pill mill legislation, and improved access to drug treatment, among many others. Hence, there may be an interaction between reformulation, prevention initiatives and interventions, and prescribing practices. One perspective to inform the extent of this limitation is to examine demand for OxyContin. Our results suggest that the desirability of OxyContin decreased as indicated by concurrent decreased prescription volume, decreased diversion and reduction in street price. The street price of the original formulation fell 57% from 2011 to 2015. Furthermore, the Drug Diversion program found a 85.6% reduction in OxyContin diversion by 2015-Q2, so the price decreased while diversion also decreased, suggesting markedly reduced demand for OxyContin.

The decrease in price for the original formulation of OxyContin was unexpected since classic supply and demand theory would indicate that a very desirable drug with decreased supply should



**Fig. 4.** Relative change in rate of abuse endorsement, Opioid Treatment Program, 2009 – 2015. The Other Opioid Group is comprised of immediate release (IR) oxycodone, IR and extended release (ER) hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxymorphone, and IR and ER tapentadol. The period of time indicated by shading was excluded from statistical analysis. CI – 95% Confidence intervals. (A) Rate adjusted for population. (B) Rate adjusted for prescription volume.

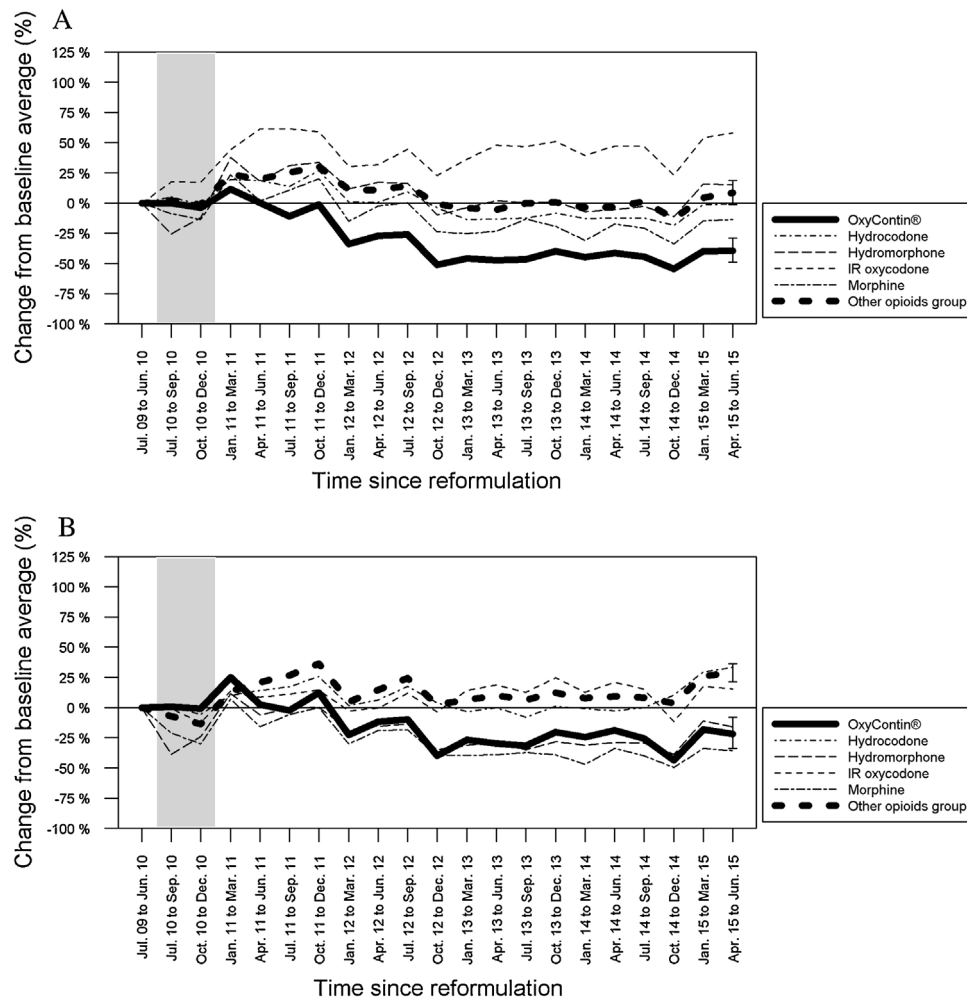
result in a higher price. However, there are several factors that likely undermined the price of the original formulation. First, it is likely that buyers realized that the original formulation was no longer produced and that there are many counterfeit products posing as the original formulation. Also important is the growing availability and affordability of potent heroin.

Overall, OxyContin demonstrated the greatest relative decrease in rates of abuse and diversion of all opioid groups throughout the study period. As importantly, the time course of change in the various opioid groups was different. OxyContin prescriptions, diversion, and abuse all decreased abruptly, within months or one year after its reformulation depending on the program. The initial steep decrease was followed by a more gradual decrease. During the initial decrease, it is likely that there were no major confounders acting to reduce diversion and abuse of OxyContin. There were undoubtedly a multitude of small interventions like drug take-back days and news stories in the popular press that may have affected perceptions of prescription opioid abuse in general. However, to our knowledge, no major interventions occurred in late 2010 or early 2011 that would be expected to selectively decrease OxyContin diversion and abuse. Therefore, we conclude that the initial decrease was largely caused by a decrease in abuse and diversion caused by reformulation of OxyContin.

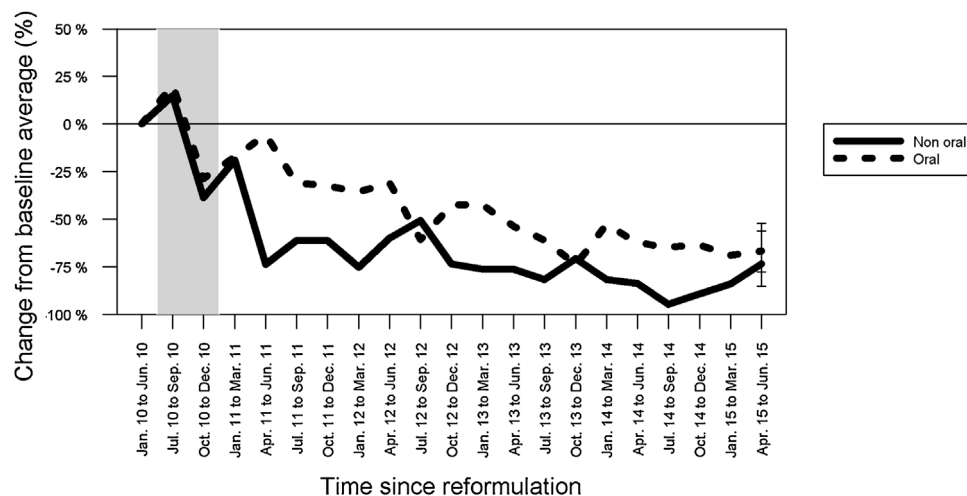
The possibility that these changes were caused by reformulation is reinforced by the observed increase in prescriptions dispensed

as well as an increase in abuse and diversion for the Other Opioid group from 2010 to 2012. After increasing, the Other Opioid group then plateaued and decreased through mid-2015. This observation suggests that prescribing patterns and abuse behaviors switched initially toward the other opioid analgesics, primarily immediate release oxycodone, hydromorphone and morphine before other factors reduced the abuse of those products as well. This interpretation is supported by the fact that rates adjusted for population showed the greatest increases, but rates adjusted for prescription volume were less affected, indicating that abuse per unit of drug did not increase substantially, just the amount of drug dispensed.

The route of abuse as represented by the Poison Center Program indicates that both oral and non-oral routes of abuse decreased although the decrease in non-oral abuse was greater. This result may seem paradoxical as observers have predicted that ADFs should affect primarily nasal insufflation or injection. (United States Food and Drug Administration, 2015; Leece et al., 2015) The progression from swallowing to snorting or injection is often viewed as unidirectional with snorting or injection displacing oral abuse. However, research indicates most abusers endorse both oral and non-oral use, perhaps depending on their desire and needs at the time of abuse as well as the environment of abuse (Katz et al., 2011; Surratt et al., 2011). Furthermore, most studies do not collect data on chewing, which is a common form of tampering. In poison centers, chewing is classified as oral. Therefore, decreased abuse in a



**Fig. 5.** Change in rate of abuse endorsement, Survey of Key Informant Patients, 2009–2015. The Other Opioid Group is comprised of immediate release (IR) oxycodone, IR and extended release (ER) hydrocodone, IR and ER morphine, IR and ER hydromorphone, IR and ER tramadol, IR and ER oxymorphone, and IR and ER tapentadol. The period of time indicated by shading was excluded from statistical analysis. CI – 95% Confidence intervals. (A) Rate adjusted for population. (B) Rate adjusted for prescription volume.

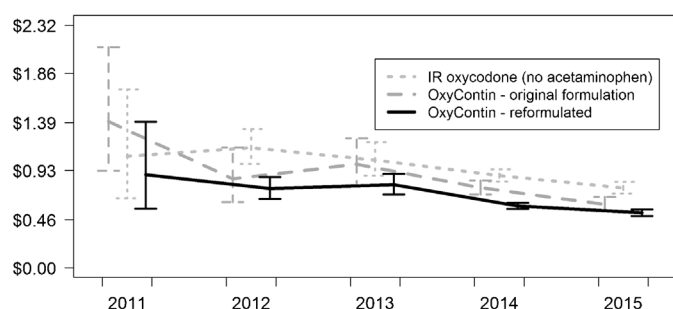


**Fig. 6.** Change in route of exposure in poison center cases involving OxyContin after reformulation. The category of oral route includes swallowing tablet whole, dissolving in mouth, and chewing then swallowing. Category of non-oral route includes injection or inhalation. The period of time indicated by shading was excluded from statistical analysis.

non-oral route would be expected to reduce concomitant use by swallowing intact or chewing and swallowing, which would then reduce the number of oral abuse events as well.

Our analysis has several limitations. Morphine extended release has been proposed as an appropriate comparator for oxycodone extended release because it comprises a large part of the extended





**Fig. 7.** Reported street price trends of oxycodone products on StreetRx.com. SE = single entity. IR = immediate release formulations.

release opioid market. We chose a compound endpoint of the group of Other Opioids because morphine alone is a poor choice for a comparator. The primary concern is that abusers identify immediate release oxycodone, hydromorphone, and oxycodone, rather than morphine, as the drugs they use when OxyContin is not available (Cicero and Ellis, 2015). Also important is the fact that the morphine market is highly influenced in recent years by increased in low-abuse risk populations because it is increasingly required by health plans to be used before OxyContin. Since OxyContin abusers have reported switching to a variety of prescription opioid analgesics, we concluded that the most defensible position is to include all of the opioids together and then to break out the major generic categories for investigators to interpret for themselves.

Another limitation of the poison center and street price data is spontaneous reporting. Various factors may influence the decision for someone to contact these programs. Data from the Poison Center, Opioid Treatment, Survey of Key Informants' Patients and StreetRx programs are based on self-reported information with all the limitations inherent to that process such as misidentification by the abuser. The extent of this misidentification is unknown, but is the lowest for the Drug Diversion program because the investigator often has the tablet for identification. These biases are not thought to vary substantially over time. Each program has been in operation for many years and there were not changes in the programs that coincided with decreased rates of OxyContin diversion or abuse. Furthermore, the trends from these programs have lasted for 5 years, have substantial magnitude and are consistent with our data from treatment programs and with the medical literature. Nevertheless, the potential for confounding is present.

Despite methods to circumvent the abuse deterrent mechanism, abuse and diversion of OxyContin decreased promptly following the introduction of a crush- and solubility- resistant formulation and continued to decrease over the subsequent 5 years. Part of the response may be explained by a general decrease in abuse and diversion of opioid analgesics in general. The temporal profile of an abrupt decrease in prescription volume and rates of diversion and abuse as well as supporting evidence of decreased non-oral abuse and street price and similar results in the medical literature support the conclusion that the reformulation of OxyContin decreased its abuse and diversion.

There are currently few products with FDA-approved labeling that includes statements about abuse deterrent properties. Of these, only OxyContin has a sufficient number of dispensed prescriptions to measure it in postmarketing surveillance systems. Essentially all data from several sources indicate its effectiveness in reducing diversion and abuse of OxyContin itself. It may have an effect on the abuse of extended release opioid analgesics as a group since those products are also experiencing a decrease (Dart et al., 2015). However, the effect on overall abuse of all opioid analgesics is unlikely to be measurable because extended release



**Fig. 8.** Trends of Endorsement for past year nonmedical use of OxyContin in National Survey of Drug Use and Health.

The number of past year endorsements for each year are plotted by year: 2004–2014. The vertical line indicates introduction of reformulated OxyContin.

2013: <http://archive.samhsa.gov/data/NSDUH/2013SummNatFindDetTables/DetTabs/NSDUH-DetTabsSect1peTabs1to46-2013.htm#tab1.1a>, page 120

2012: <http://archive.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/DetTabs/NSDUH-DetTabsSect1peTabs1to46-2012.htm#tab1.1a>

2011: <http://archive.samhsa.gov/data/NSDUH/2011SummNatFindDetTables/NSDUH-DetTabsPDFWHTML2011/2k11DetailedTabs/Web/HTML/NSDUH-DetTabsSect1peTabs1to46-2011.htm#Tab1.1A>

2010: <http://archive.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2010R/HTML/Sect1peTabs1to46.htm#Tab1.1A>

2009: <http://archive.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2009R/HTML/Sect1peTabs1to46.htm#Tab1.1A>

2008: <http://archive.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2008R/HTML/Sect1peTabs1to46.htm#Tab1.1A>

2007: <http://archive.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2007R/HTML/Sect1peTabs1to46.htm#Tab1.1A>

2006: <http://archive.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2006R/HTML/Sect1peTabs1to46.htm#Tab1.1A>

2005: <http://archive.samhsa.gov/data/NSDUH/2k5nsduh/tabs/Sect1peTabs1to66.htm#Tab1.1A>

2004: <http://archive.samhsa.gov/data/NSDUH/2k4nsduh/2k4tabs/Sect1peTabs1to66.htm#tab1.1a>

Data were obtained from the detailed tables published by Substance Abuse and Mental Health Services Administration for 2010–2014:

opioids represent a small part of the opioid market. In order to properly understand the impact of abuse deterrent opioids, most of the opioid market needs to be comprised of ADF products.

## Conflict of interest

S. Geoff Severtson, PhD, is an employee of Denver Health and Hospital Authority. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Matthew S. Ellis, MPE, receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Steven P. Kurtz, PhD, receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Andrew Rosenblum, PhD, receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Theodore J. Cicero, PhD, receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Mark W. Parrino, MPA, receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Michael K. Gilbert, MPH, is an employee of Epidemico, a wholly-owned subsidiary of Booz Allen Hamilton that receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Mance E. Buttram, PhD, receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

Nabarun Dasgupta, PhD, is an employee of Epidemico, a wholly-owned subsidiary of Booz Allen Hamilton that receives research funding from Denver Health – RADARS System. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. RADARS System is the property of Denver Health and Hospital Authority, a political subdivision of the State of Colorado (public hospital for Denver, Colorado). The subscribers receive data, but do not participate in developing the System, participate in data col-

lection, analysis or reporting, nor do they have access to the raw data.

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This analysis presents analysis of RADARS System data. Most manufacturers of prescription opioid analgesics or stimulants have subscription contracts to receive data from RADARS System. The subscribers receive data, but do not participate in developing the System, participate in data collection, analysis or reporting, nor do they have access to the raw data.

## Contributors

S. Geoffrey Severtson, PhD was the primary author of the manuscript and performed the statistical analyses.

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Andrew Rosenblum, PhD collected the data from the Opioid Treatment Program and reviewed and edited the manuscript.

Theodore J. Cicero, PhD, collected the data from the Survey of Key Informant Patients and reviewed and edited the manuscript.

Mark W. Parrino, MPA collected the data from the Opioid Treatment Program and reviewed and edited the manuscript.

Michael K. Gilbert, MPH, collected the data from the StreetRx Program and reviewed and edited the manuscript.

Mance E. Buttram, PhD collected the data from the Drug Diversion Program and reviewed and edited the manuscript.

Nabarun Dasgupta, PhD collected the data from the StreetRx Program and reviewed and edited the manuscript.

Becki BucherBartelson, PhD performed the statistical analyses and reviewed and edited the manuscript.

Jody L. Green, PhD performed the statistical analyses and reviewed and edited the manuscript.

Richard C. Dart, MD, PhD, supervised the project, co-wrote the manuscript, and reviewed and edited the manuscript.

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